ATTACHMENTS

1. Abstract for Rodriguez-Villar et al. (1997);

2. Abstract for Dozio et al. (1997);

3. Abstract for Suehiro et al. (2005);

4. Abstract for Bergman et al. (1997);

5. Abstract for Standl E. (1995);

6. Copy of front page and claims of US 6,689,359;

7. GB-A-2429013;

8. WO 2007/017686;

9. Copy of http://www.diabetes.org/pre-diabetes/pre-diabetes-symptoms.jsp; and

10. Copy of http://www.jewishhospitalcincinnati.com/cholesterol/insulin_resistance.htm.

11. Copy of front page and claims of US 6,689,359 B1

ELSEVIER Links
FULL-TEXT ARTICLE

High proinsulin levels in late PRE-IDDM stage.

Rodriguez-Villar C, Conget I, Casamitjana R, Vidal J, Manzanares JM, Gomis R.

Endocrinology and Diabetes Unit, Universitat de Barcelona, Spain.

AIM: To analyse the fasting proinsulin levels in first degree relatives of patients with insulin-dependent diabetes mellitus (IDDM) with different risk for developing the disease. PATIENTS AND METHODS: Non siblings first degree relatives, 33, of IDDM patients were separated into three groups with different risk for developing IDDM: Group 1, 14 first degree relatives (eight male/six female), aged from 18 to 57 years, normal first phase insulin release (FPIR) in the intravenous glucose tolerance test, negative ICA; Group 2, 11 first degree relatives (six male/five female), aged from 16 to 62 years, normal FPIR and ICA < 20 JDF U; Group 3, eight first degree (six male/two female), from 16 to 52 years, FPIR diminished and ICA > 20 JDF U. All patients had normal oral glucose tolerance test at the initiation of the study. We tested fasting proinsulin (PRO) and insulin (IRI) levels by radioimmunoassay (RIA) and the PRO/IRI ratio. RESULTS: Four first degree from the group 3 developed IDDM after 2-32 months. No differences were observed in-fasting PRO levels and PRO/IRI ratio between the groups. However, the PRO (21.7 +/- 5.8 pmol/l) and PRO/IRI ratio (0.29 +/- 0.10) levels of the subjects who developed IDDM were significantly higher (P < 0.05) than those values obtained in subjects who did not developed the disease. CONCLUSION: these data indicate that fasting PRO levels and the PRO/IRI ratio may be an additional marker in post-puberty first-degree relatives of IDDM patients with immunological and metabolic evidence of high risk for developing the disease.

Low prevalence of islet autoantibodies in patients with gestational diabetes mellitus.

Dozio N, Beretta A, Belloni C, Castiglioni M, Rosa S, Bosi E, Bonifacio E.

Department of Medicine, H. San Raffaele Scientific Institute, University of Milano, Italy. dozion@imihsra.it

OBJECTIVE: To determine the proportion of patients with gestational diabetes mellitus (GDM) who have serological characteristics typical of IDDM. RESEARCH DESIGN AND METHODS: Islet cell antibodies (ICAs), insulin autoantibodies (IAAs), GAD65, and IA-2 antibodies were measured in 145 pregnant women with GDM, 33 with impaired glucose tolerance (IGT), and in 73 with normal glucose tolerance (NGT). ICAs were measured by indirect immunofluorescence; GAD65 and IA-2 antibodies, by a radio-ligand immunoassay incorporating 35S-labeled recombinant antigen; and IAAs, by a liquid-phase radiobinding assay. RESULTS: The prevalences of islet autoantibodies were low and not significantly different between groups. ICAs were detected at levels ranging from 5 to 45 Juvenile Diabetes Foundation U in 14 (10%) women with GDM, 2 (6%) women with (GT, and in 4 (5%) women with NGT. IAAs were detected at levels between 3 and 4 SD above the mean in 4 (3%) women with GDM, 0 women with IGT, and in 1 (1%) woman with NGT. None had both ICAs and IAAs. Neither GAD65 nor IA-2 antibodies, which have been detected in the majority of pre-IDDM and IDDM patients, were found in NGT, IGT, or GDM patients. CONCLUSIONS: Low-titer ICAs and IAAs are not infrequent in pregnant women, but multiple islet autoantibodies and antibodies to GAD65 or IA-2 were not found in GDM. These findings suggest that the serological characteristics of IDDM are rare in GDM.

Hyperinsulinemia in patients with colorectal cancer.

Suehiro T, Matsumata T, Shikada Y, Sugimachi K.

Department of General Surgical Science, Graduate School of Medicine,
Gunma University, Gunma, Japan. tsuehiro@med.gunma-u.ac.jp

BACKGROUND/AIMS: It has been reported that non-insulin
dependent diabetes mellitus (NIDDM) is one of the risk factors for
colorectal cancer. Usually, in the pre-NIDDM state,
hyperinsulinemia is seen for 5 to 8 years. Insulin is the growth
factor of epithelial and cancer cells of colon and rectum. In this
study, we evaluate glucose tolerance in the patients with
colorectal cancer who were never diagnosed with DM.
METHODOLOGY: We studied 82 patients with colon cancer who
were never diagnosed with DM. 75-g glucose tolerance test (75g
GTT) was performed and we measured serum glucose (BS) and
insulin (IRI) levels, and we defined them as normal glucose
tolerance (NGT), impaired GT (IGT), and DM. We also defined
hyperinsulinemia as highest IRI levels over 100mU/mL at 75g
GTT. RESULTS: Serum glucose and insulin levels were higher in
the patients with colorectal cancer than in healthy controls. In 82
colorectal cancer patients, 39 were IGT and 5 were DM. All DM
patients also had hyperinsulinemia. Only 14 patients (17%) had
NGT and normal IRI levels. CONCLUSIONS: Our findings suggest
that hyperinsulinemia is occasionally seen in patients with
colorectal cancer. Hyperinsulinemia may be one of the causes of
colorectal cancer and we have to control hyperinsulinemia to
prevent recurrence of colorectal cancer even after curative
resection.

Toward an integrated phenotype in pre-NIDDM.

Bergman RN, **Watanabe R**, **Rebrin K**, **Ader M**, **Steil G**.

Department of Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles 90033, USA.

The search for the genetic basis of NIDDM has magnified the need for an efficient representation of the pre-NIDDM phenotype. The overall goal is to relate specific mutations on the genome to specific changes in physiologic function which lead to NIDDM. Unfortunately, there is still not a clear understanding of the molecular cause of NIDDM in most individuals. Therefore, one must take an alternative approach: to express in quantitative terms the various tissue processes which determine the ability to regulate the blood glucose in fasting and after carbohydrate administration. A minimal list of such processes includes the provision of glucose by the liver, insulin sensitivity, insulin secretion, and glucose effectiveness. The latter function is the ability of glucose per se to enhance glucose disappearance from blood, independent of a dynamic insulin response. Approaches to measuring the list of functions which determine the glucose tolerance are reviewed: they include the minimal model method, which quantitates insulin sensitivity (SI) and glucose effectiveness (SG), and a combined model approach, which measures insulin secretion. These methods are being developed for large populations. Such a development is important for elucidating the causes of reduced glucose tolerance in populations, and examining the relation between such causes and outcomes including diabetes and cardiovascular disease. Of particular importance for diabetes development is the characteristic hyperbolic relationship between insulin secretion and insulin action. This relationship, the "hyperbolic law of glucose tolerance' indicates that insulin secretion can only be assessed in terms of the ambient degree of insulin sensitivity. By applying this principle, it is clear that latent pancreatic islet-cell dysfunction has been underestimated, and may be significant even in subjects with impaired glucose tolerance. Finally, new explorations of insulin control of liver glucose output indicate that this process may be under the control of free fatty acids. The latter realization indicates that the insulin effect on lipolysis is what is critical for determination of glucose output in the fasting state, and that insulin resistance at the level of the adipocyte may determine the extent of fasting hyperglycaemia, and may be an important factor in the overall phenotype in prediabetic and NIDDM individuals.

Links

Hyperinsulinemia and atherosclerosis.

Standl E.

Third Medical Department, City Hospital Schwabing, Munich, Germany.

Studies of macrovascular disease in non-insulin-dependent
diabetes (NIDDM) have shown a significant increase in
peripheral vascular, coronary, and carotid artery disease in
diabetics compared to non-diabetics. This prevalence appears to
be related to insulin levels and to the degree of hyperinsulinemia
as measured in the blood of these patients. Indeed, a cluster of
markers, including hyperinsulinemia, insulin resistance,
hypertension, dyslipoproteinemia, and a high waist-hip ratio,
has been associated with NIDDM and increased risk for
macrovascular disease. Variously described as Metabolic
Syndrome or Syndrome X, this syndrome may be operative for
many years before NIDDM is diagnosed. Given the complexity of
Metabolic Syndrome, a single-factor intervention for preventing
macrovascular disease in NIDDM is unlikely. However, it seems
advisable to screen, on a regular basis, all patients presenting a
pre-NIDDM state, as well as those with overt NIDDM, for
pertinent cardiovascular risk parameters and for emerging
macrovascular disease. It is suggested that any attempt to
prevent macrovascular disease in subjects with glucose
intolerance should aim at decreasing insulin resistance and
hyperinsulinemia.